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The plasma level of some amino acids and physical and mental fatigue

E. A. Newsholme[a] and E. Blomstrand[b]

[a]*Cellular Nutrition Research Group, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU (United Kingdom), Fax +44 1865 275 259*
[b]*Pripps Research Laboratory, Pripps Bryggerier, Bromma (Sweden)*

Abstract. Tryptophan is converted to 5-hydroxytryptamine (5-HT) in the brain and evidence is presented that an increase in the concentration of 5-HT can result in physical and mental fatigue during prolonged exercise. The entry of tryptophan in the brain is influenced by the plasma level of free tryptophan (that not bound to albumin) and, from competition for entry into brain, by the plasma level of branched chain amino acids. Hence, oral administration of branched chain amino acids could, theoretically, prevent the increase in 5-HT level during exercise and therefore delay physical and mental fatigue. Evidence in support of this hypothesis is presented.
Key words. Tryptophan; 5-hydroxytryptamine; fatigue; branched chain amino acids; exercise.

Introduction

Fatigue is defined physiologically as the inability to maintain the expected power output. It is of importance for all of the population, from the elite athlete to the patient suffering from injury, viral infection, surgery or chronic fatigue syndrome. Much of the extensive research into factors causing fatigue has been done by physiologists and biochemists who are primarily interested in either nerves and nervous function, the mechanism of excitation-contraction coupling or the chemical and biophysical aspects of energy provision for the cross-bridge cycling in muscle. Another field of biochemistry, which has only recently been applied to exercise, is that of metabolic-control-logic. This logic will be applied to our knowledge of amino acid metabolism in brain to suggest a novel cause of fatigue. From current knowledge, there are at least five main *metabolic* causes of fatigue: the first three causes relate directly to the muscle, but the last two probably involve the brain. These causes of fatigue are as follows: a) the depletion of phosphocreatine in muscle; b) the accumulation of protons in muscle; c) the depletion of glycogen in muscle; d) the decrease of the blood glucose concentration; e) an increase in the concentration ratio of the free tryptophan to branched-chain amino acids in the bloodstream.

It is important to note that these factors are not mutually exclusive, although how they cause fatigue at the individual motor unit level is not known: it is even remotely possible that they all have a common molecular mechanism within the muscle.

The plasma concentration ratio of free tryptophan/branched chain amino acids andcentral fatigue

In this review, we will focus upon a recent and novel suggestion[10] that changes in plasma amino acid concentrations could play a role in central fatigue by increasing the rate of synthesis and hence the level of the neurotransmitter 5-hydroxytryptamine (5-HT) in some parts of the brain. Thus, it is suggested that this neurotransmitter is involved in the central fatigue, that is, it increases the sensitivity of the brain to other signals of fatigue and makes the athletes (subjects) decrease their physical activity.

The following is a summary of several important points that form the basis for the hypothesis that links changes in the plasma levels of some amino acids to changes in the brain that could result in central fatigue.

- Tryptophan is converted in the brain to the neurotransmitter 5-hydroxytryptamine (5-HT).
- Both branched-chain amino acids (leucine, isoleucine and valine) and tryptophan enter the brain upon the same amino acid carrier, so that competition between the two types of amino acids for entry into brain can occur[8].
- None of the enzymes involved in the conversion of tryptophan to 5-HT appears to approach saturation with substrate (i.e. there is no flux-generating step in this series of reactions)[8] (see ref. 11 for a discussion of the concept of the flux-generating step).
- An increased level of tryptophan in the brain will, therefore, be expected to increase the rate of formation of 5-HT and hence increase the level of this neurotransmitter. This could result in increased firing of some 5-HT neurones and this might result in central fatigue since it is known that 5-HT is involved in sleep.
- Tryptophan is unique amongst the amino acids in that it is bound to plasma albumin, so that it exists as a bound and a free form, which are in equilibrium: it is considered that the free concentration is that which competes with branched chain amino acids for entry into the brain. The plasma level of free tryptophan

increases when the plasma fatty acid level is increased. This is caused by the binding of fatty acids to albumin. It is predicted that the plasma concentration of free tryptophan influences the entry of tryptophan into the brain. Thus, it is predicted that an increase in the plasma concentration of free tryptophan would increase the brain concentration of 5-HT and this would result in central fatigue.

- The plasma concentration ratio, free tryptophan/branched-chain amino acids, is increased in man and in the rat after prolonged and exhaustive exercise[3,4,13].
- In the rats, the levels of tryptophan were increased by exhaustive exercise in all areas of the brain studied: in contrast, the level of 5-HT was increased in only two areas, the brain stem and the hypothalamus: the level of 5-hydroxyindole acetic acid, the degradation product of 5-HT, was also increased in these areas[4].

In exercise, either intermittent or continuous, there is elevation in the blood catecholamine level and a decrease in that of insulin which will result in fatty acid mobilization from adipose tissue. This will result in an increase in the plasma fatty acid level. If there is precise control between the mobilization of fatty acids from adipose tissue, the extent of vasodilation in muscle, and the stimulation of fatty acid oxidation within muscle, the increased rate of fatty acid oxidation by muscle may occur without much, if any, of an increase in the plasma level of fatty acids. Hence, this will not influence the free tryptophan level. However, if the co-ordination between the increased rate of release of fatty acids and the increased rate of utilisation by active muscle is poor – due, for example, to lack of training – the blood fatty acid concentration could be increased sufficiently that the plasma concentration of free tryptophan is increased. Furthermore, in intermittent exercise in which there is usually a greater dependence upon 'anaerobic' exercise and, therefore, less opportunity to oxidise these fatty acids, the plasma level of fatty acid could rise and hence increase the concentration of free tryptophan. A large increase in the plasma fatty acid level could also occur in response to hypoglycaemia which will, via changes in hormone levels, encourage a greater rate of fatty acid mobilisation from adipose tissue.

Since branched-chain amino acids are not taken up by liver but by muscle, upon ingestion they are not removed by the liver so that their plasma concentration is rapidly increased. This can, therefore, maintain the resting plasma free tryptophan/branched chain amino acid concentration ratio during exercise. Is this important?

- In a Stockholm marathon, 193 volunteers were randomly divided into two groups and the experiment was performed double-blind. In the experimental group, a drink containing a mixture of branched-chain amino acids was given four times during the race and the other group was given a placebo drink. Considering the whole group of subjects, the difference in performance between the experimental and placebo groups was small and did not reach significant levels. However, when the subjects were divided into two subgroups based on their time to finish the marathon, the performance was statistically significantly better for the slower runners (3.05–3.30 h to complete this marathon) in the experimental group compared with the placebo group. The difference in time at this pace would mean an improvement in performance of 5–6 min[5]. [The reason for the lack of effect on performance in the faster runners (< 3.05 h to complete this marathon) is not known. It might be that the more well-trained (faster) runners are more resistant to fatigue – both central and peripheral fatigue – and therefore less sensitive to a supply of branched chain amino acids. Alternatively, the slower runners may be less well-trained so that co-ordination between the control of fatty acid mobilisation from adipose tissue and its utilization by muscle is poor, resulting in a marked elevation of the plasma fatty acid level. In this case, it would be expected that the plasma free tryptophan/branched-chain amino acid concentration ratio would increase earlier in the race and this would be expected to raise the brain 5-HT level and fatigue would be the result. For this reason, the effect of the amino acid supplementation would be easier to detect in these slower runners.]
- Eight runners completed two 24 km cross-country runs separated in time by one week. After each race the runners were asked to recall their perceived physical and mental effort. On the first occasion four subjects drank the placebo drink before the run and after 13 km into the run, and four subjects drank the branched-chain amino acids at the same time periods. The placebo and the branched-chain amino acid drinks were then switched and the procedure repeated one week later. There was no difference in running time between the two occasions. However, both the perceived physical and mental efforts were lower when branched-chain amino acids were taken, but the difference was only statistically significant for the perceived mental effort[12].
- Twenty-four participants, who agreed to volunteer for the experiment, were questioned after a marathon on their mental attitude towards the race. All of the 12 participants who drank the placebo drink during the race experienced aversion to running the race during the last 10 km; in contrast, of the 12 participants who drank the branched-chain amino acids, only seven experienced aversion to running the race in the last 10 km. The difference was statistically significant[12].
- The Stroop colour and word test (CWT) was given to 16 subjects who participated in a 30 km cross-country race[6]. [Research on the CWT has established that

the test provides a useful tool in the study of neuropsychological and cognitive processes.] In the group who took the branched-chain amino acids during the race, the performance in this test improved after the race in comparison with before the race, while no statistically significant difference was found for the subjects who took the placebo drink.

- Administration of a 5-HT agonist to rats impairs running performance in a concentration related manner[1]. In contrast, administration of a 5-HT antagonist to the rats improved running performance[7].
- Administration of a 5-HT re-uptake blocker to human subjects lowered physical performance – exercise time to exhaustion during standardized exercise was decreased in comparison to a control condition[14].
- The sensitivity to a neurotransmitter can be modified by changing the number of receptors on the postsynaptic neurone. Since the release of prolactin from the pituitary is controlled, in part, by the activity of the 5-HT system in the hypothalamus, the prolactin release mechanism can be used as test of 5-HT sensitivity in that part of the brain. This sensitivity has been found to be lower in endurance-trained athletes compared with untrained individuals[9]. This suggests that one effect of endurance training is to decrease the sensitivity of the 5-HT post synaptic receptor system. Hence, any increase in the level of 5-HT in the synapse will have a smaller effect on fatigue compared to untrained subjects. It will be interesting to know if this change is secondary to chronic increases in synaptic 5-HT levels as a result of increased levels of plasma free tryptophan during prolonged training periods or a specific effect of training on the number of 5-HT receptors in the post-synaptic nerones.

Thus, effects of BCAA supplementation on physical and mental fatigue may depend not only on the changes in the plasma free tryptophan concentrations but also on the sensitivity of the 5-HT system to changes in the level of 5-HT in neurones in specific parts of the brain.

Although all of the recent discussion of 5-HT levels and fatigue has focused attention on fatigue in relation to performance of athletes, this should not conceal the potential clinical importance of this work. Fatigue is a factor that can decrease the rate of recovery and increase the length of stay in hospital of patients after surgery, injury or infection. And it may be of considerable importance that the cause of chronic fatigue syndrome is still unknown; it is of interest that there is some evidence of an increased number of 5-HT receptors in the hypothalamus in such patients[2]. The concept that changes in the plasma amino acid concentration may play a role in fatigue opens up a new line of investigation in several important clinical conditions.

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